Biomimetic Synthesis of Meroterpenoid Natural Products Using Dearomatization Strategies

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DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Henry Patrick Pepper Date

LIST OF ABBREVIATIONS

AIBN	Azobisizobutyronitrile
aq	Aqueous
ATP	Adenosine Triphosphate
BCG	*Mycobacteria Bovis*
BRSM	Based on Recovered Starting Material
bs	Broad Singlet
CAM	Ceric Ammonium Molybdate
CAN	Ceric Ammonium Nitrate
CA SC5314	*Candia Abicans* SC5314
CD	Circular Dichroism
CoA	Coenzyme A
COSY	Correlated Spectroscopy
cm^{-1}	Wavenumber(s)
d	Doublet
DDT	*para*-Dichlorodiphenyltrichloroethane
DBE	Double Bond Equivalence
DBU	1,8-Diazabicycloundec-7-ene
DDQ	2,3-Dichloro-5,6-Dicyano-1,4-Benzoquinone
DEAD	Diethyl Azodicarboxylate
DHP	3,4-Dihydro-*2H*-pyran

DIBAL-H	Diisobutylaluminium Hydride
DMSO	Dimethyl Sulfoxide
DMF	*N*,*N*-dimethylformamide
dppf	1,1'-Bis(diphenyphosphino)ferrocene
EDDA	Ethylenediaminediacetate
EI	Electron Impact
ESI	Electrospray Ionization
EtOAc	Ethyl Acetate
Grubbs II	Grubbs' Second Generation Catalyst
h	hour(s)
HMBC	Heteronuclear Multiple Bond Connectivity
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High Performance Liquid Chromatography
IC_{50}	Half Maximal Inhibitory Concentration
IR	Infrared Spectrum
J	Coupling Constant
KHMDS	Potassium Hexamethyldisilazide
LDA	Lithium Diisopropylamide
m	Multiplet
m/z	Mass Units

MES	2-(*N*-methylmorpholino)-ethanesulfonic Acid
MIC	Minimum Inhibitory Concentration
MOM	Methoxymethyl
mp	Melting Point
MPAP	Monocyclic Polyprenylated Acylphloroglucinol
MRSA	Methicillin Resistant *Staphylococcus Aureus*
MS	Mass Spectrum
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NaHMDS	Sodium Hexamethyldisilazide
NMP	*N*-methyl-2-Pyrrolidine
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
PA01	*Pseudomonas Aeruginosa*
PI3K	Phosphatidylinositol 3-Kinase
PPAP	Polycyclic Polyprenylated Acylphloroglucinol
PP	Pyrophosphate
ppm	Parts Per Million
PPTS	Pyridinium *para*-Toluenesulfonate
p-TsOH	*para*-Toluenesulfonic Acid

q	quartet
R_f	Retention Factor
ROESY	Rotating Frame Nuclear Overhauser Effect Spectroscopy
s	Singlet
SA	*Staphylococcus Aureus*
SAR	Structure Activity Relationship
rt	Room Temperature
t	Triplet
TBS	*tert*-Butyltrimethylsilyl
TBAF	Tetrabutylammonium Fluoride
TES	Triethylsilyl
Tf	Trifluoromethylsulfonate
THC	Tetrahydrocannabinol
THF	Tetrahydrofuran
THN	1,3,6,8-Tetrahydroxynaphthalene
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
UV	Ultraviolet Light
VHPO	Vanadium Dependent Haloperoxidase

ABSTRACT

Synthetic efforts towards various meroterpenoid natural products based on biosynthetic speculation were undertaken in order to gain biosynthetic insight and to develop efficient syntheses of some structurally complex, biologically active compounds.

The first total synthesis of the PPAP natural product garcibracteatone was achieved in four linear steps from phloroglucinol (0.6% overall yield). The key biomimetic synthetic step was an oxidative radical cyclization cascade reaction, where four new carbon-carbon bonds, four new carbocyclic rings and five new stereocentres were formed in the one step.

The first total synthesis of merochlorin A was achieved in five linear steps from methyl-3,5-dimethoxyphenylacetate (6% overall yield). The key biomimetic synthetic step was a [5 + 2] cycloaddition reaction induced be oxidative dearomatization to form the bicyclo[3.2.1]octane core.

The first total synthesis of the napyradiomycin natural product naphthomevalin was achieved in 11 steps from methyl-3,5-dimethoxyphenylacetate (1.4% overall yield). The key biomimetic synthetic step was a thermal α-ketol rearrangement reaction to form the naphthoquinone core of the napyradiomycins. The synthetic naphthomevalin was additionally converted into A80915G *via* a biomimetic S_N2 epoxidation reaction, and into napyradiomycin A1 *via* a chemoenzymatic reaction.